REMARKS

Claim 38 has been amended to remove reference to SEQ ID NO:2 thus providing correct antecedent basis for the recombinant FGF-2 recited in this claim. No new matter is added by way of claim amendment.

Applicant acknowledges with appreciation the Examiner's withdrawal of the rejections of the claims under 35 U.S.C. §102(b). Applicant wishes to bring to the attention of the Examiner copending U.S. Application Serial No. 09/417,721, filed October 13, 1999, which also claims the benefit of U.S. Provisional Application No. 60/104,103, filed October 13, 1998.

Claims 10-67 are pending in the application. Applicant respectfully requests reexamination and reconsideration of the pending claims in light of the claim amendment and discussion herein. The Examiner's remarks in the Office Action are addressed below in the order set forth therein.

The Rejection of Claim 38 under 35 U.S.C. 112, Second Paragraph, Should Be Withdrawn

Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as lacking antecedent basis for the recitation of SEQ ID NO:2. Claim 38 has been amended to remove reference to SEQ ID NO:2. As proper antecedent basis for recitation of recombinant FGF-2 or recitation of angiogenically active fragment or mutein of a recombinant FGF-2 resides in the base claim, Applicant respectfully submits that this rejection is overcome and should be withdrawn.

The Rejection of the Claims under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 10-67 stand rejected under 103(a) as being unpatentable over Franco, U.S. Patent No. 4,378,347 (the "Franco patent") in view of Sellke *et al.* (1998) *Soc. Thoracic Surgeons* 65:1540-1544 (the "Sellke *et al.* reference") and Uchida *et al.* (December 1995) *Amer. Heart J.* 130(6):1182-1188 (the "Uchida *et al.* reference). This rejection is respectfully traversed.

The present invention is directed to administration of recombinant FGF-2 or administration of an angiogenically active fragment or mutein of a recombinant FGF-2 directly into one or more coronary vessels or directly into a peripheral vein of a human patient to promote angiogenesis in a patient suffering from coronary artery disease (CAD), to treat CAD, to treat

myocardial infarction, and to provide relief from the symptoms of angina in a patient in need of such relief. As previously noted, the invention is based on a clinical trial with 66 participants at phase I. Applicant has definitively demonstrated the prolonged therapeutic benefit of administering recombinant FGF-2 into one or more coronary vessels or into a peripheral vein of a human patient having CAD. One mode of administering this growth factor is by infusion. For reasons already of record and as discussed further herein, Applicant submits that the cited references alone or in combination do not teach or suggest administration of recombinant FGF-2 or administration of an angiogenically active fragment or mutein of a recombinant FGF-2 directly into one or more coronary vessels or into a peripheral vein to treat human patients in accordance with the methods of the present invention.

To establish a *prima facie* case of obviousness (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. MPEP §2143. Applicants respectfully submit that when establishing a *prima facie* case of obviousness, one must consider the teachings of the cited reference(s) as a whole, including portions that would lead away from the claimed invention. MPEP §2141.02. It is Applicant's contention that a *prima facie* case of obviousness has not been established in the present application for reasons already of record and further discussed herein.

The Franco patent discloses an effective dose of about 10 μg to 1 gm of basic FGF (bFGF) per 100 grams of heart tissue for use in treating the heart after myocardial infarction or for use in combination with heart surgery procedures such as coronary bypass operations. This reference does not teach or suggest administration of bFGF, or administration of an angiogenically active fragment or mutein of bFGF, into one or more coronary arteries of a human patient for the treatment of CAD, for the treatment of a myocardial infarction, for promoting angiogenesis in the heart of the patient, or to provide the patient with relief from symptoms of angina.

Rather, the Franco patent teaches that direct injection into the heart is the first preferred mode of administering the effective dose of bFGF for treatment of myocardial infarction or for

use in combination with heart surgery procedures. This is in fact the only mode of administration demonstrated by this reference. Furthermore, efficacy of this mode of administration is only demonstrated in preclinical canine and feline models of acute myocardial infarction. As previously noted by Applicant in the Amendment dated June 4, 2001, at page 10, lines 3-7, these animal models are not predictive of Applicant's claimed method for treating coronary artery disease, which is a chronic rather than an acute ischemic condition. One cannot extrapolate from the results of myocardial injection of bFGF in an animal model of acute myocardial infarction to a method for treating a human patient with coronary artery disease.

The Franco patent suggests intravenous injection as the second preferred mode of administration of bFGF for the treatment of myocardial infarction or for use in combination with heart surgery procedures. However, this reference fails to demonstrate the intravenous mode of bFGF administration in any animal model of acute myocardial infarction, much less the successful use of bFGF in this manner. The Examiner has stated that efficacy is not relevant to the issue of obviousness, "because a mere teaching or suggestion of the claimed method is all that is required to render the invention as obvious" (Office Action dated September 7, 2001, at page 6, lines 6-7 of item 7). However, to establish a *prima facie* case of obviousness, the reference alone, or in combination with other references, must not only teach or suggest to one of skill in the art the modification that must be undertaken to arrive at Applicant's invention, but must also provide to one of skill in the art a reasonable expectation of success. Further, where multiple references are relied upon to demonstrate obviousness of a claimed invention, there must be some motivation to combine the references in order to arrive at Applicant's invention.

Applicant respectfully submits that Franco's mere suggestion of intravenous injection of bFGF as a means of treating acute myocardial infarction or for use in combination with heart surgery procedures does not provide one of skill in the art with a reasonable expectation of success for Applicant's method of administering a recombinant FGF-2 into one or more coronary arteries or into a peripheral vein of a human patient for the treatment of CAD, the treatment of a myocardial infarction, for promoting angiogenesis in the heart of the patient, or providing the patient with relief from symptoms of angina. Furthermore, that reasonable expectation of

success cannot be provided by either the Uchida *et al.* reference or the Sellke *et al.* reference for reasons noted below.

Further, the Franco patent provides no guidance whatsoever with respect to administration of bFGF into a peripheral vein as is required by those embodiments of Applicant's claimed invention that are encompassed by intravenous administration. Thus, the Franco reference fails to teach or suggest all of the limitations recited in the pending claims.

The Examiner relies upon the combination of the Franco reference with the Sellke *et al.* and Uchida *et al.* reference to support the obviousness rejection in the Office Action. However, Applicant contends that one of skill in the art would not have been motivated to combine the teachings of these references to arrive at Applicant's claimed invention as those supporting references also fail to provide the guidance lacking in Franco that is necessary to arrive at Applicant's claimed invention.

Uchida *et al.* is directed to intrapericardial injection of bFGF plus heparin sulfate in a canine model of acute myocardial infarction. As noted for the animal models relied upon in the Franco reference, results from the animal model in the Uchida *et al.* reference cannot be extrapolated to treatment of a human patient for a chronic ischemic condition such as CAD. In fact, Uchida *et al.* themselves do not attempt to make this extrapolation, but instead focus the analysis of their results on the potential impact for patients with myocardial infarction. Furthermore, this reference also makes no mention whatsoever of direct administration of bFGF or angiogenically active fragment or mutein of bFGF into a peripheral vein for treatment of CAD or myocardial infarction.

Though Uchida *et al.* cite to a prior study with intracoronary injection of bFGF in a canine model of acute myocardial infarction, they counter with the statement that "in clinical situations, however, application of this therapy is limited to the patients not contraindicated to coronary angiography" (Uchida *et al.* (1995) at page 1182, column 2, lines 8-10). Applicant again directs the Examiner to Uchida *et al.* at page 1182, column 2, lines 11-20, where the authors continue:

> Clinically, all three coronary arteries are involved in one third to two thirds of the patients with coronary artery disease. In these patients the bFGF injected into the coronary artery *may not reach the infarcted area, may be conjugated with the extracellular matrix at the site of coronary lesion, and may enhance stenosis.* In addition to such *limitations* bFGF administered into the coronary artery *may pass through the heart and stimulate growth of concealed neoplasmas.* (emphasis added)

These authors have purposely pointed out distinct limitations of intracoronary injection that would lead one of skill in the art away from using this mode of administration to treat acute myocardial infarction.

In response to Applicant's contention that the Uchida *et al.* reference teaches away from Applicant's claimed invention, the Examiner has stated that "Applicant's argument is limited because the reference further teaches that this method can be widely applied as a therapeutic regimen for myocardial salvage or as a preventive regimen for myocardial infarction" (Office Action dated September 7, 2001, at page 6, lines 11-13 of item 7). Applicant respectfully notes that the Examiner has misquoted the Uchida *et al.* reference. In fact, it is not intracoronary injection that the Uchida *et al.* authors are referring to in making this statement. Rather, for reasons noted below, it is the authors' preferred method of administering bFGF, i.e., intrapericardial administration, that "can be widely applied as a therapeutic regimen."

The objective of the Uchida *et al.* reference is to establish a preferred method of angiogenic therapy for acute myocardial infarction that works irrespective of coronary anatomy and irrespective of contraindications for coronary interventions and surgery. The statement made by the Uchida *et al.* authors, and the statement relied upon by the Examiner, has been taken out of context. Applicant directs the Examiner to the last 6 lines of the Abstract on page 1182 of the Uchida *et al.* reference, where Uchida *et al.* state:

> The transcatheter intrapericardial injection of bFGF plus HS caused angiogenesis and myocardial salvage. This method might bring about a selective therapeutic and preventive modality of myocardial infarction irrespective of coronary anatomy and contraindications for coronary interventions and surgery.

In the background section of the Uchida *et al.* reference, the authors point to the drawbacks of intracoronary injection of bFGF for myocardial infarction at page 1182, column 2, lines 11-20, as noted above. The authors immediately follow this discussion of the drawbacks of intracoronary injection with a statement that establishes the desirability of finding a mode of administering bFGF that provides for selective and safe delivery of bFGF "into the infarcted area *irrespective of the coronary anatomy and irrespective of contraindications for coronary interventions*" (emphasis added). Applicant directs the Examiner to page 1182, column 2, lines 20-27 of the Uchida *et al.* reference, where the authors state:

> If it is possible to administer bFGF selectively and safely into the infarcted area *irrespective of the coronary anatomy and contraindications for coronary interventions,* this method can be widely applied as a therapeutic regimen for myocardial salvage to the patients with acute myocardial infarction or as a preventive regimen for myocardial infarction. (emphasis added)

This statement encompasses the statement relied upon by the Examiner to establish the Uchida *et al.* reference as teaching that Applicant's method of administering "can be widely applied as a therapeutic regimen." When read within the proper context of the entire article, it is clear that the desirable method that "can be widely applied as a therapeutic regimen" is the intrapericardial injection method newly reported by Uchida *et al.* Hence, Uchida *et al.* conclude that their newly proposed method of administering bFGF addresses this as yet unmet need for a method of administering bFGF that works *irrespective of the coronary anatomy or contraindications to coronary interventions.* Applicant directs the Examiner to page 1187, last full paragraph prior to the references, where authors of the Uchida *et al.* reference state:

> *Intrapericardial injection* of drugs through the right atrium was very easy, and cardiac tamponade did not occur in any dogs in this study. Clinically, this approach seems very easy and can be applied to salvage infarcted myocardium *irrespective of the coronary anatomy, the age, or the presence or absence of diseases in other organs that are contraindicated to coronary interventions and coronary bypass surgery.* (emphasis added)

Thus, Applicant contends that Uchida *et al.* teach intrapericardial injection as a preferred method of administering bFGF for treatment of acute myocardial infarction and teach away from intracoronary injection as a therapy for this ischemic condition.

As previously noted in the Amendment filed June 4, 2001, the Sellke *et al.* reference teaches administration of heparin-alginate slow-release beads comprising bFGF to the epicardial fat or subepicardial tissue surrounding the heart (see Figure 1 and the points made by Applicant at pages 8-9 in the June 4, 2001 Amendment filed). This mode of administration represents an invasive surgical procedure where slow-release devices are implanted into tissue. This is an entirely different route of delivery than that claimed by Applicant. Sellke *et al.* do not teach or suggest administration of this growth factor or administration of an angiogenically active fragment or mutein of a recombinant FGF-2 into one or coronary vessels or into a peripheral vein to treat CAD, myocardial infarction, angina associated with CAD, or to promote angiogenesis in the heart of a patient in need of angiogenesis.

In summary, the Office Action relies upon the Sellke *et al.* and Uchida *et al.* references to provide the guidance to one of skill in the art as to how one can modify the Franco reference to arrive at Applicant's invention. The Franco patent teaches direct injection of bFGF into the myocardium, and merely suggests intravenous injection of bFGF with no reasonable expectation of success, for treatment of acute myocardial infarction or for use in combination with heart surgery procedures. The Franco patent fails to teach or suggest administration of bFGF into one or more coronary arteries or into a peripheral vein in the manner set forth in Applicant's claimed invention. This teaching or suggestion cannot be found within the Sellke *et al.* or Uchida *et al.* references. Contrary to the Examiner's statement on lines 3-5 or page 4 of the September 7, 2001 Office Action, Sellke *et al.* do not teach a method for treating human patients for coronary artery disease comprising "administering recombinant human b-FGF also known as FGF-2, to one or more coronary vessels (see Figure 1)" (Office Action dated September 7, 2001). This fact has been acknowledged by the Examiner's withdrawal of the rejection of the claims under 35

U.S.C. §102(b) in the September 7, 2001 Office Action in response to Applicant's remarks in the Amendment filed June 4, 2001. Finally, the Uchida *et al.* reference teaches that intrapericardial injection is the preferred mode of administering bFGF for treatment of myocardial infarction and teaches away from administration of recombinant FGF-2 directly into one or more coronary arteries in the manner set forth in Applicant's claimed invention.

Thus, given the state of the art at the time of Applicant's invention, one of skill in the art would not have been motivated to combine these three references to arrive at Applicant's invention, nor would a reasonable expectation of success have been supported by any of the cited references. Further, these cited references alone or in combination do not teach or suggest all of the limitations recited in the pending claims. For all of these reasons, Applicant respectfully submits that a *prima facie* case of obviousness has not been established.

As the cited references do not teach or suggest the claimed invention, Applicant respectfully submits that this rejection of the claims should be withdrawn.

CONCLUSION

In view of the above amendment and remarks, Applicant submits that the rejection of the claims under 35 U.S.C. §103(a) is overcome. Applicant respectfully submits that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required

therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to Examiner Hope Robinson at the Patent and Trademark Office at facsimile number (703) 308-4242, on January 7, 2002.

Tracey Wright
Tracey Wright

Version with Markings to Show Changes Made:

In the Claims:

Please amend claim 38 as follows:

38. (amended) The method of claim 10, wherein said therapeutically effective amount of said recombinant FGF-2 [of SEQ ID NO: 2] or [an]said angiogenically active fragment or mutein thereof is administered by infusion.